Perspective

Neoadjuvant chemotherapy versus chemoradiation for esophageal cancer: no survival difference does not mean no differences

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Abstract: The current standard of care for locally advanced esophageal and gastroesophageal junction cancer is neoadjuvant therapy, yet controversy remains regarding whether chemotherapy or chemoradiation should be the treatment of choice. The literature is broad and contains conflicting reports. We seek to explore factors that impact our selection of one treatment versus the other.

Keywords: Esophageal cancer; gastroesophageal junction cancer (GE junction cancer); neoadjuvant therapy

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In the last three decades, esophageal cancer in western countries has undergone an epidemiological transition from a predominance of squamous cell histology (SCC) to now adenocarcinoma (AC) (1,2). The etiology of this shift is still not clear and cannot be explained solely by dietary changes or an increased incidence of Barrett's esophagus nor the increased awareness of tobacco and alcohol abuse leading to the significantly lower incidence of SCC (3-5).

The treatment of patients with esophageal cancer remains controversial due to several factors. The low incidence of the disease compared to, for example, breast and lung cancer (2,6,7), results in large clinical trials comparing different treatment modalities not being feasible (7). Moreover, the epidemiological shift mentioned above makes interpreting older clinical trials more challenging. Further, the difference in the disease prevalence, incidence and prognosis between eastern *vs*. western countries coupled with the stage migration following the integration of PET scans and EUS in both staging and treatment makes the problem even more complicated (2,7). Another very important issue is the classification of the gastroesophageal (GE) junction tumors and the inclusion of Siewert I tumors in the gastric studies and Siewert III tumors in the esophageal studies (2,8).

Since the publication of the MAGIC trial in 2006 (9) and the CROSS trial in 2012 (10), neoadjuvant treatment (NAT) has become the standard of care for the management of patients with locally advanced tumors of the GE junction and the distal esophagus (11,12). These two landmark publications clearly describe the clinical benefits of such an approach, especially given the significant overall survival improvements. These trials also brought to light the importance of the concept of complete pathologic response (pCR) as a biomarker for improved outcomes in patients receiving NAT (9,10,13). The overlap of these two trials is related to the fact that 11% of patients in the MAGIC trial had tumors located in the gastroesophageal junction compared with 22% of patient treated on the CROSS trial, leading to some confusion with respect to the most appropriate treatment for such patients, which is further intensified since the clinical determination of tumor location between distal esophageal tumors, GE junction tumors and proximal gastric tumors is a difficult clinical endeavor (9,10).

With this in mind, Samson and colleagues have performed a review of the National Comprehensive Cancer Database (NCDB) and compared the outcomes of patients receiving neoadjuvant chemotherapy versus

neoadjuvant chemoradiation (14). Keeping in mind the retrospective nature of this analysis and the limitations of this national database, these results need to be interpreted with caution. Selection bias was clear in the patient characteristics, with patients who received neoadjuvant concurrent chemotherapy and radiation being younger (P=0.02), predominantly Caucasian (P=0.049) and largely those who lived in an urban setting (14). Patients treated in recent years were more likely to receive chemotherapy and radiation following the release of the CROSS trial data even in abstract form in national and international meetings.

Not surprisingly, patients with more advanced disease (T2 or higher or N+) were more likely to receive neoadjuvant chemotherapy and radiation. Given the inherent selection bias, it is expected that patients receiving neoadjuvant chemotherapy and radiation would be more likely to have a R0 resection and a pCR. The minimal impact of the type of neoadjuvant therapy on post-surgical complications is consistent with previously published papers (15). Several factors might play a role in post-surgical complications, including the level of surgical expertise, the type of radiation and even the delivery and the type of chemotherapy agents used. The authors concluded on Kaplan-Meier analysis that achieving pCR was significantly associated with an improved overall survival of 59.5±4.0 *vs.* 30.1±0.76 months for those with residual disease, P<0.001 which is expected; however they found that despite a significant improvement in pCR rate, receiving neoadjuvant chemoradiation therapy did not significantly impact the overall mortality hazard (HR =1.12; 95% CI: 0.97–1.30, P=0.12) (14). Acknowledging the limitations of this study is crucial. Indeed, the retrospective nature of the data, the small number of patients who received chemotherapy only, the variability in the chemotherapy received, the dose of radiation, the type of radiation, and the percentage of patients who finished treatment, should all be factored into the equation (14). Although the role of adjuvant therapy is still in question in this patient population, some patients with residual disease received adjuvant therapy which could also increase the variability.

Several retrospective series have reported conflicting results about the role of neoadjuvant radiation in the treatment of esophageal cancer (16-18). These retrospective studies are hypothesis generating and should not change practice patterns. The authors also cited a recently published multicenter randomized clinical trial of neoadjuvant chemotherapy *vs.* chemoradiation for esophageal cancer in Europe; the trial concluded that radiation therapy was associated with a higher pCR rate and higher complete (R0) resection and lower LN metastasis which did not translate into better overall PFS or 3 year survival (19). The authors failed to mention that the above trial accrued 181 patients only and the primary end point was histological compete response. The trial met its primary end point supporting the addition of radiation leading to improved pCR, however, the trial was not powered to assess overall survival (14,19).

Additional factors that elude this type of analysis that should be considered are the clinical difficulty to receive chemoradiation after esophagectomy. Therefore, we consider strategies to improve pCR rates to provide patients with the potential for significant improvements in survival.

Conclusions

Neoadjuvant therapy for cancer of the distal esophagus and the gastroesophageal junction (Siwert I-II) remains the standard of care. Neoadjuvant chemoradiation remains associated with better surgical outcomes and improved pathologic complete responses. Strategies to improve pCR will eventually lead to improving outcomes in patients with esophageal cancer. Large, prospective, well designed clinical trials are needed to answer the questions on the best approach for this patient population with stratification by tumor location and pathology.

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Footnote

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